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Lung Cancer Etiology: Challenges of the Future

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In a recent review of the etiology of lung cancer we discussed several questions (61). These were: [1] the reported shift toward an increasing proportion of adenocarcinoma compared to squamous cell carcinoma of the lung in men, [2] the probable protective effect of green vegetables and fruits, especially β-carotene and vitamin A, against the induction of lung cancer, and [3] the possibility of a tumor enhancing effect of dietary fats. Other aspects considered were [4] the relative contribution of tumor initiators and tumor promoters in tobacco carcinogenesis, [5] the effect of the low-yield cigarette on the reduction of the risk of cancer of the larynx and lung, and [6] the risk of the "passive smoker" to develop lung cancer. Finally, we discussed current and future efforts toward reducing the number of smokers among the adolescent and adult population and educational methods for preventing young people from starting the smoking habit. In this communication we will focus on the question of the low-yield cigarette and on the epidemiology of lung cancer in nonsmokers.

RECOMMENDATIONS FOR FUTURE STUDIES

Histologic Pattern

An examination of pathology reports after lung cancer surgery demonstrates a noticeable lack of uniformity among pathologists as to their classification of the lesions (65,70). Changes in diagnostic techniques and classification systems, improvements in treatment, as well as the aggressiveness of the physician may all contribute to secular differences in histologic patterns (41,53,54,61). For instance, some pathologists who are interested in a specific type of lung cancer will employ various histological techniques for the identification of that lesion, whereas other pathologists will be satisfied with reporting the cancer as a "bronchiogenic carcinoma." When a pathological diagnosis

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has both etiologic and prognostic implications, minimum standards should be followed regarding an acceptable histologic definition. An organized body of pathologists should set up a list of criteria, such as a refinement of the *Atlas of Tumor Pathology* already in use (2), to be used as a guide in interpreting slides.

Our findings, based in large part on data obtained from Memorial Sloan-Kettering Cancer Center, which has uniform standards of diagnosis, suggest a significant trend towards glandular lung cancer, especially in males (Table 1), the natural history of which requires investigation. One possible source of this shift might be the general decline in the sales-weighted tar yield of cigarettes sold on the market since about 1964 (46). Smokers who switch to lower yield cigarettes tend to compensate for the low nicotine delivery by smoking more intensely and inhaling more deeply (51). This may have an effect on the incidence of peripherally located lesions.

Metabolism Studies

Currently, there is an increased interest regarding the role of dietary fat, vitamin A, retinoids and other micronutrients in the etiology of lung cancer (7,21). A recent report indicating that dietary fat enhances benzo(a)pyrene-induced lung cancer in rats provides an experimental basis for its role in the etiology of this cancer (3). Differences in the tumor promoting effects of various types of dietary fat should be studied experimentally as we have done for breast and colon cancer (11,32). In the case of mammary cancer, the risk associated with the consumption of unsaturated fats in rats is higher than that associated with the consumption of saturated fats (9). No increase in the risk of breast or colon cancer is linked to the use of monounsaturated fats (11,42). There are many conceivable mechanisms for the enhancement of carcinogenesis by fat, and these may vary by cancer site. Although it appears that cholesterol does not play a role in the etiology of lung cancer (58), it is possible that changes in the ratio of saturated to unsaturated fatty acids may increase cell membrane permeability, rendering the cells more susceptible to carcinogenic stimuli (16). Lipoproteins of all classes suppress the immunologic capacity of lymphocytes (16), and may saturate macrophages in the lung (19), thus impairing immunologic host-defenses against carcinogens. These hypotheses need to be explored by both the epidemiologist and the laboratory scientist.